Introduction

The scientific basis of the HyperQ technology consists of numerous studies that have been published in leading cardiology journals over the past three decades. Extensive research efforts, including computer modeling[1], animal experiments[2] as well as dedicated studies in humans[3-5], provide a sound scientific basis for the ability to identify myocardial ischemia using analysis of the high-frequency components in the mid-QRS complex of the ECG. A comprehensive literature review and references can be found in BSP's White Paper no. 2. The purpose of this review is to describe the clinical evidence of the HyperQ technology in detecting ischemic heart disease.

Clinical Studies

Recent clinical studies aimed at showing the diagnostic value of the HyperQ System are detailed below. Visit our website for a complete list of studies.

HyperQ vs. ST segment analysis in patients undergoing exercise nuclear scan – A preliminary validation study was carried out at the Charleston Area Medical Center, West Virginia, in collaboration with Duke University. In this study, HyperQ-based ischemia detection was compared to ST segment analysis in 133 patients (100 men, age 63±12 years) undergoing exercise nuclear scan, which was used as the gold standard of ischemia. Compared to ST segment analysis, the HyperQ index of ischemia was found to be more sensitive (79% vs. 41%, p<0.05) and more specific (71% vs. 57%, p<0.05). In women, HyperQ analysis resulted in significantly improved specificity relative to conventional ECG (70% vs. 33%, p<0.05)[6] due to the known underperformance of conventional ECG in the women population compared to the sustained superior performance of HyperQ regardless of gender.

HyperQ vs. ST segment analysis in 996 patients referred for nuclear scan – HyperQ and ST deviations were evaluated in 996 (670 men, age 58.9±10.2 years) consecutive patients referred for exercise nuclear scan, which was used as the gold standard of ischemia. HyperQ response correlated with severity of ischemia (Fig 1A). Compared with ST segment analysis, HyperQ analysis was appreciably more sensitive (69% vs. 39%, P<0.005) while also being more specific (86% vs. 82%, P<0.05).

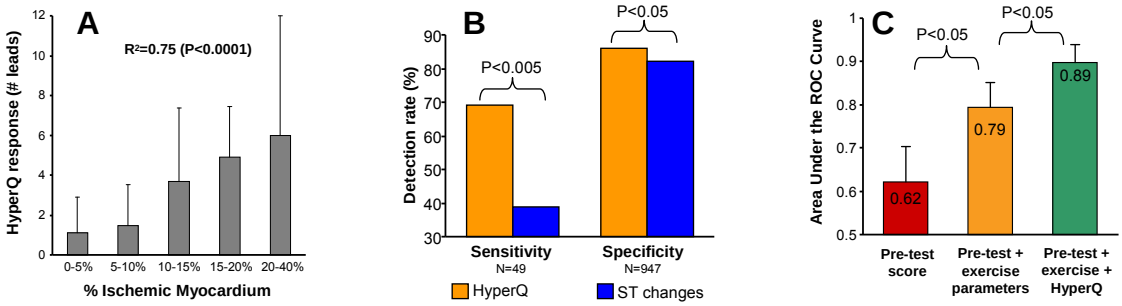

Figure 1: **A**: Number of leads with abnormal HyperQ response vs. severity of ischemia. **B**: The diagnostic indices of the HyperQ and ST segment analyses. **C**: ROC curves for logistic regression models that include i) pre-test score, ii) pre-test score and exercise parameters and iii) pre-test score, exercise parameters and HyperQ response.

Multivariate logistic regression indicated considerable incremental diagnostic value of HyperQ over pre-test likelihood of CAD and exercise parameters (Fig 1C)[7].

HyperQ vs. ST segment analysis in women referred for coronary angiography - The study aimed to test the diagnostic performance of HyperQ and conventional exercise ECG in detecting stress-induced ischemia in women referred for non-urgent coronary angiography, which was used as the gold standard for comparison. Patient group consisted of 113 women (age 64±9 years), who performed symptom-limited treadmill exercise ECG test prior to their angiography. HyperQ analysis provided sensitivity of 70% and specificity of 80% for detection of angiographically significant coronary obstruction. HyperQ was more specific than exercise ECG test (80% vs. 50%, P<0.005), as well as more accurate (76% vs. 62%, P<0.01). The number of leads with ischemic HyperQ response correlated with the severity of CAD. HyperQ was highly specific (93%) in patients who achieved their age-predicted

target heart rate, and retained its diagnostic accuracy in subgroups of patients with resting ECG abnormalities or inconclusive exercise ECG[8].

Improved detection of ischemic heart disease by combining high-frequency ECG analysis with stress echocardiography – The study evaluated the clinical usefulness of HyperQ analysis during exercise echocardiography in 175 patients (age 57±9, 118 men) who performed stress echocardiography, followed by either coronary angiography (n=64) or computed tomography (CT) angiography (n=111). CAD (≥70% occlusion of a major coronary artery) was determined by either invasive angiography or CT angiography. The HyperQ analysis was more sensitive compared to ST segment analysis (71% vs. 44%, N=34, P<0.05) with similar specificity (76% vs. 73%, N=141, P=NS). Logistic regression models indicated that the HyperQ data had incremental diagnostic value over clinical variables, exercise parameters and echocardiography data. The combined regression model of HyperQ-echocardiography test provided sensitivity of 91% and specificity of 76%[9].

HyperQ analysis in patients with acute myocardial infarction - The purpose of the study was to quantitatively characterize the morphological patterns of the HyperQ signals in patients with acute myocardial infarction (AMI), and to describe the trend of these patterns following reperfusion. Resting five-minute high-resolution ECG was acquired from 30 patients (age 55±11 yrs, 26 men) upon their admission to the intensive cardiac care unit. Serial ECGs were acquired following coronary revascularization and after additional 24 hours. HyperQ analysis was used to compute a high-frequency morphology index (HFMI), which quantifies the extent of ischemic patterns. HFMI values were significantly higher on the admission ECG as compared to the post-intervention ECG (4.6±2.9 vs. 3.4±2.3, P<0.05) and to the 24h ECG (4.6±2.9 vs. 2.8±2.1, P<0.01). In 79% of the patients who were successfully revascularized HFMI value decreased from admission ECG to 24h ECG[10].

On-Going Studies

In-progress clinical studies involving the HyperQ technology are detailed below.

- **Incremental diagnostic accuracy of HyperQ for ischemia identification in patients referred for exercise myocardial perfusion imaging** (PI: Dr. Jamieson Bourque, University of Virginia, Charlottesville, VA). The study compares HyperQ to standard ST-segment analysis for identification of any and significant (≥10%) left ventricular ischemia by exercise SPECT myocardial perfusion imaging. Interim analysis of 292 consecutive patients (mean age 59.6, 65% men) HyperQ had substantially higher sensitivity than ST-segment depression for both any (63% vs. 18.5%, P<0.001) and significant ischemia (82.4% vs. 35.3%, P<0.001). The specificities of HyperQ and ST-segment analysis were similar (84.9% vs. 86.6%)[11].
- **The usefulness of HyperQ analysis in the evaluation of patients presenting to the emergency department with chest pain** (PI: Prof. Doron Zahger, Soroka Medical Center, Be'er-Sheva, Israel). The study includes patients with chest pain suspected to be of ischemic origin. Resting high-frequency ECG is recorded upon presentation to the emergency department. HyperQ-based diagnosis is compared to conventional ECG interpretation, using the discharge diagnosis and one-month follow-up as the reference gold standard[12,13]. Interim analysis of 187 patients (age 60±13 years, 65% men) showed that the high-frequency morphology index (HFMI) was significantly higher in patients with ACS, compared to non-ischemic. HyperQ analysis provided sensitivity and specificity of 63% and 74%, respectively. HyperQ was more sensitive than ECG in detecting non ST-elevation ACS (62% vs. 30%, P<0.001).
- **Early detection and monitoring of myocardial ischemia using analysis of high frequency ECG component** (PI: Prof. Christian Mueller, University Hospital Basel, Switzerland). This study is carried out as part of a joint project with Schiller AG and University Hospital Basel, funded through the Eurostars-EUREKA program. High resolution 16-lead ECG is acquired from consecutive patients with suspected acute myocardial ischemia at the emergency department. The diagnostic performance of HyperQ analysis in detecting ACS will be evaluated using the final diagnosis as gold-standard.

Selected Bibliography

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(See website for full list)